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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 08/482,402 | 06/07/95 | RAPOPORT | B 102105.151CI |

| EXAMINER | |
|---|---|
| UNGAR, S | |
| **ART UNIT** | **PAPER NUMBER** |
| 1642 | 28 |

HM12/0613

QUEST DIAGNOSTICS, INC.
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**DATE MAILED:** 06/13/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

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**UNITED STATES DEPARTMENT OF COMMERCE**
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09/482,402

| APPLICATION NUMBER | FILING DATE | FIRST NAMED APPLICANT | ATTORNEY DOCKET NO. |
|---|---|---|---|

| EXAMINER | |
|---|---|
| ART UNIT | PAPER NUMBER |
| 1647 | |

**DATE MAILED:**

## INTERVIEW SUMMARY

All participants (applicant, applicant's representative, PTO personnel):

(1) Susan Ungar (3) _____

(2) Quon Nguyen (4) _____

Date of Interview 6/6/00

Type: ☐ Telephonic ☐ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☐ No If yes, brief description: _____

Agreement ☐ was reached. ☐ was not reached. NA

Claim(s) discussed: NA

Identification of prior art discussed: _____

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: After Final is being reviewed, a courtesy copy of PTO form 303 will be faxed to Stan Wise at 949-[redacted]-725-4957 on 6/7/00

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

1. ☐ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary. A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has are ready been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

Examiner Note: You must sign this form unless it is an attachment to another form.

FORM **PTOL-413** (REV.1-96)

Quon Nguyen

Inventions of Group I and the newly added claims as disclosed are biologically and chemically distinct, unrelated in structure and function, made by and used in different methods and are therefore distinct inventions.

***Specification***

3. The objections to the specification recited in Paper No. 12, Sections 5, 6, 7 and 8 are maintained for the reasons set forth in Paper No. 25, page 2, Section 6.

***Oath/Declaration***

4. Objection to the Declaration recited in Paper No. 25, page 3, Section 7 is maintained.

***New Grounds of Rejection***

***Claim Rejections 35 USC 112***

5. Claims 38-46 and 48-56 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of a recombinant DNA sequence encoding a human thyroid peroxidase which is recognized by a disease associated antibody has no clear support in the specification and the claims as originally filed. A review of the specification discloses support for a recombinant DNA sequence encoding a human thyroid peroxidase which is immunoprecipitated by sera from Hashimoto's serum (p. 59). However, there is no support for or even a contemplation of binding by any disease associated antibody other than sera associated with Hashimoto's disease. The subject matter claimed in claims 38-46 and 48-56 broadens the scope of the invention as originally disclosed in the specification.

6. Claims 38-46 and 48-56 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 38-46 and 48-56 are indefinite because claims 38 and 48 recite the phrase "disease associated antibody". The claims are confusing because it is not clear whether the claim is drawn to autoantibodies or to any antibody that binds to thyroid peroxidase which is associated with a disease or even what a disease associated antibody is meant to be, thus the metes and bounds of the claim cannot be determined.

***Claim Rejections - 35 USC § 102***

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claim 38 is rejected under 35 U.S.C. § 102(b) as being anticipated by Libert et al, of record as evidenced by Rapoport (Annual Rev.Med., 1991, 42:91-96).

Because of the indefinite nature of the claim language, it is assumed for examination purposes that "disease associated antibody" is any antibody that binds to thyroid peroxidase because thyroid peroxidase is associated with disease.

Rapoport teaches that thyroid peroxidase is the "microsomal antigen" and the recognized target of autoimmune Hashimoto's thyroiditis (see abstract).

The claim is drawn to a recombinant sequence encoding human thyroid peroxidase which is recognized by a disease associated antibody.

Libert et al teach as set forth previously. One of ordinary skill would instantly envision the encoded protein which would be expected to bind to disease associated antibodies such as those produced by the autoimmune disease Hashimoto's thyroiditis. Although the reference does not specifically teach that the encoded protein is recognized by a disease associated antibody, the protein encoded by the claimed recombinant sequence appears to be the same as the protein encoded by the prior art product, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

***Claim Rejections - 35 USC § 103***

9. Claims 38-46 and 48-56 are rejected under 35 USC 103 essentially for the reasons previously set forth in Paper No. 12, Section 16, pages 9-11, Paper No. 17, Section 10, pages 5-6), Paper No. 20, Section 12, pages 5-6 and Paper No. 25, section 9, pages 3-6.

Because of the indefinite nature of the claim language, it is assumed for examination purposes that "disease associated antibody" is any antibody that binds to thyroid peroxidase because thyroid peroxidase is associated with disease.

The claims are drawn to a recombinant DNA sequence encoding a human thyroid peroxidase which is recognized by a disease associated antibody, wherein the sequence possesses a stop codon upsteam from a transmembrane domain, wherein the encoded peroxidase is secreted from a cell and is recognized by a disease associated antibody, a vector which comprises the DNA sequence and a host cell transformed with said vector.

Seto et al, of record, or Libert et al of record, in view of Lee et al of record, or Ellis et al of record, EP 0139 417 of record, or Rose et al of record, and Magnusson et al of record teach as previously set forth.

EP 0139417 teaches as set forth previously and further specifically teaches that the truncated polypeptide encoded by the recombinant DNA has the same antigenic determinants as the membrane bound polypeptide and is a truncated, membrane-free derivative of the membrane-bound polypeptide. The derivative is formed by omission of a membrane-binding domain from the polypeptide, allowing it to be secreted from the recombinant host cell system in which it has been produced (p. 5, lines 25-32). Further, immunization of mice with the secreted polypeptide resulted in the production of sera which bound to and neutralized full length antigen *in vitro*. Immunization with the secreted polypeptide resulted in protection against disease from the native antigen (pgs.27-31). Clearly, since protection against disease inherently requires the formation of disease associated antibodies and these antibodies were synthesized in response to the secreted antigen, it would be expected that not only the wild-type antigen but also the secreted polypeptide would bind to these antibodies. Further, it was demonstrated that the truncated, secreted polypeptide bound to the same monoclonal antibodies used

for the full length antigen (p. 31(a)). Thus it is clear that the recombinantly made truncated and secretable form of the transmembrane protein retains both its structure and function as well as its ability to bind antibodies bound by the full length protein.

Rose et al teach as set forth previously and further teach that the G protein has been widely studied as a model integral membrane protein and as previously disclosed, teach the production of a truncated, secretable polypeptide derived from the integral membrane protein. (p. 753, col 2). Further, Rose et al teach that antibodies that bind to the full length protein also bind to the truncated, secretable variant (p. 756, col 2 and 758, cols 1 and 2). Thus it is clear that the recombinantly made truncated and secretable form of the transmembrane protein retains its structure as well as its ability to bind antibodies bound by the full length protein.

It would have been *prima facie* obvious to one of ordinary skill in the art and one of ordinary skill in the art would have been motivated to produce the truncated secretable polypeptide of the combined references for the reasons previously set forth. One of ordinary skill in the art would have had a reasonable expectation that the truncated secretable polypeptide would bind to disease associated antibodies because both EP 0139417 and Rose et al teach that truncated, secretable transmembrane proteins retain the structure and antibody binding capabilities of the full length native antigen. Thus one of ordinary skill would have had a reasonable expectation of success of encoding a truncated secretable antigen, with the recombinant DNA sequence of the combined references, that would bind to disease associated antigens.

The Applicant argues that the (a) newly added claims cannot be rejected if the prior references or the combination of prior references do not show that there was a

reasonable expectation of success that a recombinant DNA could encode a truncated hTPO that may be recognized by antibodies associated with a disease, for example Hashimoto's disease, (b) Applicant cites a general reference, Bowie et al, to demonstrate the unpredictability of protein chemistry and to call into question the ability of the encoded truncated secretable polypeptide of the combined references to bind antibodies bound by native antibody, (c) Applicant cites Wadsworth et al to demonstrate that a single amino acid alteration to a thyroid stimulating hormone receptor completely alters its function, implicating that its three dimensional structure changes with a single amino acid alteration.

The arguments have been considered but have not been found persuasive because (a') the combined references demonstrate a reasonable expectation of success for the reasons set forth above, further, as drawn to Hashimoto disease-associated antibodies, Applicant is arguing limitations not recited in the claims as currently constituted, (b') it is clear, as set forth above, that it would be expected that recombinant truncated secretable membrane proteins would retain both structure and the ability to bind to antibody which binds to the full length protein, (c') although the Wadsworth et al reference clearly demonstrates that the replace of a cysteine (which would be expected to form a disulfide bond and therefore be critical to the structure of the binding site) with a serine alters the capability of receptor to bind ligand, however, it is clear, as set forth above, that as drawn specifically to encoded recombinant truncated secretable membrane proteins, it would be expected that the encoded recombinant truncated secretable membrane proteins would retain both structure and the ability to bind to antibody which binds to the full length protein.

10. All other objections and rejections recited in Paper No. 25 are withdrawn.

11. No claims allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
August 16, 2000